Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The long view

The coronavirus could end up mild like a common cold

Anthony King

POLICY-MAKERS are scrabbling to contain the spread of the coronavirus, as more highly transmissible variants travel around the world. Yet the evolution of SARS-CoV-2 in this way comes as no surprise to virologists. In fact, it is probably just one step on a much longer evolutionary trajectory. In time, virologists predict, the virus will become more benign, following an evolutionary pathway previously taken by four other human coronaviruses that today cause nothing more than the "common cold". How could this happen, and how will our actions play a part?

Coronaviruses tend to evolve slowly compared with other RNA viruses because they proofread their genetic material as they replicate, so can filter out mutations. What's more, SARS-CoV-2 isn't currently under much pressure to change, says virologist Ralph Baric at the University of North Carolina at Chapel Hill. It is successfully colonising a new species – with an open banquet of hosts – and variants that spread faster are outcompeting others.

But evolutionary pressures are starting to kick in. As the virus encounters increasing resistance from antibodies among people who have been infected or vaccinated, new mutations become more likely to take hold. Indeed, some experts suggest that the new variants we currently see arose inside the bodies of people with long-lasting infections.

Lab studies back up this idea. "Some of these variants emerged in vitro when the virus was cultured for several days in the presence of convalescent plasma," says Manuela Sironi, an evolutionary virologist at the Scientific Institute IRCCS Eugenio Medea in Italy.

We don't know exactly what mutations might increase the speed at which the virus can spread. SARS-CoV-2 has four main structural proteins, including the spike protein that sticks out from its surface and helps it attach to cells in the body, as well as non-structural proteins that hijack the machinery inside host cells.

Changes in transmission would probably involve mutations in the spike, which is targeted by the vaccines, says Sironi.

It is impossible to say which mutations would make SARS-CoV-2 more or less deadly. "That is more casino than science at the moment," says Marc Van Ranst at KU Leuven in Belgium. "There are a gazillion possible mutations."

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Familiar trajectory

It is also difficult to predict whether SARS-CoV-2 will evolve to be more harmful, says Sironi. But Van Ranst is optimistic. "Its aim is not to kill us or make us sick," he says. "The virus is successful when it is unnoticed and gets transmitted easily."

Most virologists tend to agree, suspecting that SARS-CoV-2 will follow a similar evolutionary trajectory to the four endemic coronaviruses that cause the "common cold", prosaically called 229E, HKU1, NL63 and OC43.

Covid-19

Why eradication is unlikely

VACCINE roll-out in a growing number of countries should eventually allow life to return to normal, but it is unlikely that we will be able to eradicate the coronavirus that causes covid-19 altogether.

"I don't see that these vaccines will be eliminating SARS-CoV-2 any time in the coming years," says Kingston Mills at Trinity College Dublin.

Despite the many variants, the coronavirus mutates less than many other viruses. "It does not seem to be as mutable a virus as influenza," says Mills. That means we shouldn't need to update vaccines every year, although occasional tweaks might be required.

Despite this, wiping out the virus will be really hard even if we manage to vaccinate most people. To stop a disease spreading, infected individuals must pass it on to less than one other person on average.

Early in the pandemic, infected people were infecting around three others on average, leading to estimates that two out of three people, or 67 per cent, need to be immune to halt transmission. This is what we mean by herd immunity.

Some people now think 70 to 90 per cent of the population may have to be immune to achieve this,

"Even vaccinating everyone on the planet might not stop the coronavirus circulating"

especially with more transmissible variants. This could be hard to do. Some covid-19 vaccines don't reach this level of effectiveness when it comes to preventing disease.

What is more, it isn't yet clear to what extent any of the vaccines prevent transmissible infections, as opposed to merely preventing symptoms, although this is still being investigated.

A few vaccines, such as the one for whooping cough, prevent symptoms, but don't block transmission, says Mills.

People at a supermarket in Germany using face masks to protect against covid-19

If so, we, as hosts, will be a crucial driver in this change. The key here is that people never seem to first encounter these endemic coronaviruses as adults. In 2013, scientists at the Chinese Center for Disease Control and Prevention (China CDC) in Beijing measured antibodies for these four common viruses. The type of antibodies generated by a first infection (immunoglobulin M, or IgM) were found only in children. Becoming a "common cold" is as much about us as the virus, says Baric. "My guess is that many of these common coronaviruses, if introduced directly into a very, very naive population of adults, would probably be pretty brutal."

Baric believes that as SARS-CoV-2 bumps into more resistance in adults, it may be pushed to evolve in this direction. "It is possible the virus has to change a little just to maintain itself in children," he says. It may evolve to escape immunity by being able to better replicate in the nose, and so turn into an upper respiratory infection, like the other endemic coronaviruses. These occasionally cause serious disease in children, but usually result in little more than a runny nose. "Children typically have less severe disease than adults," says Baric.

If SARS-CoV-2 follows this pattern, then it should become much less deadly. Other coronavirus infections in healthy adults are usually mild, but reoccur. A 1990 experiment revealed that adults infected with 229E were open to reinfection one year later. The China CDC antibody study also found that 70 per cent of adults had antibodies for the four endemic coronaviruses. Every two to three years, it seems people become more susceptible to these viruses, says Baric. They are re-infected, but retain enough immune memory to fight off severe disease and experience only mild symptoms. Reinfection seems to act as an immune booster.

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Endemic coronaviruses cause the common cold

"Even without relevant genetic changes, SARS-CoV-2 might eventually turn into the fifth endemic coronavirus," says Sironi.

Recent modelling by epidemiologist Jennie Lavine at Emory University in Atlanta, Georgia, and her colleagues supports this, concluding that once the virus is endemic and first exposure is in childhood, SARS-CoV-2 will be relegated to a common cold. "Primary infections tend to be more severe, especially in older people," says Lavine. "As primary infections increasingly are restricted to children, we expect the disease severity to overall become mild."

Unknown timescale

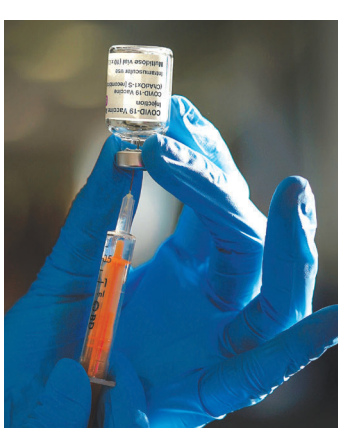
This has all happened before, according to Van Ranst, who in 2005 reported that OC43 probably jumped to people from cattle and triggered a pandemic in the late 19th century dubbed the Russian flu. The bad news is that we don't know how long it took OC43 to dilute to a common cold virus or when SARS-CoV-2 will join the endemic club. "Our model suggests that the quicker people get exposed, the quicker we get to that mild state," says Lavine. Without vaccines, that would push up deaths.

What's more, endemic coronaviruses can still cause pneumonia in older people. In 2003, when a disease ran rampant in an elderly care home in Canada and killed one in 12 of the residents that it infected, a coronavirus was suspected. It turned out to be OC43. So even a much tamer SARS-CoV-2 may still be a threat to older people for a long time to come. ▮

This means that viruses – or bacteria in the case of whooping cough – can circulate largely undetected, popping up only when they spread to unvaccinated people and cause disease.

In other words, even vaccinating everyone on the planet might not be enough to stop the coronavirus circulating at low levels, and we are unlikely to get close to this.

In some countries many people say they will refuse the vaccine, such as France, where only 4 in 10 people want it. And no vaccine is yet approved for people aged under 16, who make up a quarter of the world's population.



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While vaccines offer hope, they are no guarantee that the coronavirus will be eradicated

However, we don't have to rely entirely on vaccines to achieve herd immunity. A study by Susan Hopkins at Public Health England and her colleagues suggests that natural infection with the coronavirus provides comparable protection, reducing the risk of reinfection by 83 per cent for at least five months.

Even if we did manage to eradicate the virus in humans, it might lurk in animals and jump back into people later on. SARS-CoV-2 can infect several other species, including cats, dogs, ferrets, bats, hamsters, deers and tree shrews.

"I think this virus is here to stay," says Hopkins, who points out that the smallpox virus is the only one we have managed to eradicate, and that took many years from the start of the campaign to eliminate it. ▮

Michael Le Page